consideration of the amendment and new claim are respectfully requested

Rejections under 35 U.S.C. 112, second paragraph

Claims 1-18 have been rejected as being indefinite for failing to define the variable "A18". Applicants respectfully note that on December 2, 1996 a Preliminary Amendment was filed wherein "A18" was defined as Ser or Thr. If for some reason the Examiner is unable to locate the Preliminary Amendment, he is requested to contact the undersigned, upon which a copy of the Preliminary Amendment and stamped postcard will be sent to the Examiner.

Claims 4-7 and 8 have been rejected under 35 U.S.C 112, second paragraph as being indefinite. More specifically, claims 4-7 and 8 have been rejected as being improperly dependent on claim 2 because claim 1 recites that the sum of the variables is between 5 and 8, whereas claims 4-7 and 9 recite the sum of the variables to be lower than 5. Claims 1-4, 8 and 9 have been amended to consistently recite nonexcluding ranges for the sum of the variables. As such, withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. 102(b)

Claims 1-3, 8-9 and 11 have been rejected under 35 U.S.C. 102(b) as being anticipated by Gaudreau et al. More specifically, the Examiner asserts that the reference discloses on page 1866,

Table II, compound No. 4-8, a fatty body-hGRF(1-29)NH2 moiety, which is encompassed by the claims and which increases the hydrophobic character of the hGRF and increases GH secretion 2.4-12 fold. Applicants traverse this rejection and withdrawal thereof and reconsideration and allowance of the claims are respectfully requested.

The present invention is drawn to a chimeric fatty body-pro-GRF analog with increased biological potency, of the following general formula:

A1-A2-Asp-Ala-Ile-Phe-Thr-A8-Ser-Tyr-Arg-Lys-Val-Leu-A15-Gln-Leu-A18-Ala-Arg-Lys-Leu-Leu-A24-Asp-Ile-A27-A28-Arg-R_0

wherein,

A1 is Tyr or His;

A2 is Val or Ala;

A8 is Asn or Ser;

A15 is Ala or Gly;

A18 is Ser or Thr;

A24 is Gln or His;

A27 is Met, Ile or Nle;

A28 is Ser or Asp;

R_0 is NH2;

wherein A1 is N- or O-anchored by a hydrophobic tail of the following general formula I:

I

wherein,

G is a carbonyl, a phosphoryl, a sulfuryl or a sulfinyl group;

X is an oxygen atom, sulfur atom or an amino group (NH);

(W=Y) represents cis or trans ($CH=CR_5$);

(W'=Y') represents cis or trans (CH=CR6);

Z is an oxygen or a sulfur atom;

R_1, R_2 and R_3, independently, are selected from a hydroxyl group, a hydrogen atom, and a linear or branched C_1-C_6 alkyl group;

R_4 is a hydroxyl group, a hydrogen atom or a linear or branched C_5-C_9 alkyl group;

R_5 and R_6, independently, are a hydrogen atom or a linear or branched C_1-C_4 alkyl group;

a is 0 or 1;

b is 0 or 1;

c is 0 to 8;

d is 0 or 1;

e is 0 to 8;

f is 0 or 1;

g is 0 to 8;

h is 0 to 1;

wherein the sum of d + f = 1 or 2 and the sum of a, b, c, d, e, f, g and h is such that the hydrophobic tail of formula I has a linear main chain of between 5 and 7 atoms (C, O and/or S).

Thus, the present invention is drawn to alkene based analogs of chimeric fatty body-pro-GRF compounds having a linear main chain of between 5-7 carbons.

As noted by the Examiner, Gaudreau et al. discloses GRF analogs which are exclusively alkanes. The present compounds must contain at least one double bond in the main chain. As such, the present invention is not anticipated by Gaudreau et al.

With regard the obviousness of the present compounds over the alkanes of Gaudreau et al., the present compounds containing a double bond and having a linear main chain length of 5 to 7 carbons possess unexpected unobvious properties over those of Gaudreau et al.

Enclosed herewith is a declaration of Dr. Paul Brazeau, co-inventor of the present invention, submitted under 37 C.F.R. 1.132. The declaration of Dr. Brazeau presents comparative data with the compounds of the present invention and those of Gaudreau et al. and Coy et al.

In Experiment 1 of the declaration, an alkane-based compound of Gaudreau et al. is compared with the equivalent compound of the present invention having a double bond.

With Experiment 2 of the declaration, compounds of the prior art having either four of eight carbon main chains were compared to a compound having six carbons. While the six carbon-based compound used in the comparative studies is not encompassed by the present invention because it is an alkane based compound, it is infact a

closer comparison to the prior art than the presently claimed compounds. In addition, comparison between alkane compounds demonstrates that a portion of the superior activity seen with the hexanoyl compound over the butyryl and octanoyl compounds is a result of the chain length rather than the presence of a double bond.

Thus, as evidenced by Experiments 1 and 2, both the chain length and the presence of a double bond contribute to the unexpected, unobvious superior activity of the present compounds over those of the prior art.

Gaudreau et al. in no way disclose or suggest fatty body-pro-GRF compounds having a double bond and a linear main chain of between 5-7 carbons. Gaudreau et al. disclose alkane based compounds of 3, 4, 6 or 8 carbons. However, in Gaudreau et al. there is no suggestion of alkene based compounds or any advantages of compounds having 5 to 7 carbons.

The experiments of the declaration of Dr. Brazeau clearly demonstrate that alkene fatty body pro-GRF compounds having 5 to 7 carbons in the main chain have unexpected, unobvious activity over those of disclosed by Gaudreau et al. As such, the presently claimed compounds and methods for using thereof are clearly not obvious over Gaudreau et al.

Rejections under 35 U.S.C. 103

Claims 1-11, 13-14 and 18 have been rejected under 35 U.S.C. 103 as being unpatentable over Gaudreau et al. in view of Coy et al. and in further view of Felix et al.

Gaudreau et al. is relied on for teaching the substitution of fatty body moieties linked to the N-terminus of hGRF(1-29) and that N-terminal elongation of hGRF by 4,6 or 8 carbon atoms increased the hydrophobicity of the compound and GH secretion 2.4-12 fold. Coy et al. is relied on for teaching that N-terminal acetylation causes a 12 fold increase in potency of the peptide.

The Examiner asserts that the difference between the references and the present invention is the use of alkenes rather than alkanes with the present invention for the N-terminal elongation. However, the Examiner further maintains that one would expect alkenes having 4-8 carbons to be as effective as alkanes because of the structural similarity between alkanes and alkenes, thus rendering the present invention obvious.

Felix is relied on for teaching pharmaceutical compositions with GRF analogs and the use of such compositions for treating dwarfism and promoting wound healing.

Claims 1 and 12 have been rejected under 35 U.S.C. 103 as being obvious over Bercu in view of Gaudreau et al. or Coy et al.

Bercu is relied on for teaching a method of diagnosing growth hormone disorders using somatostatin and GHRH by inhibiting secretion of growth hormone with somatostatin and then stimulating

the pituitary gland's release of growth hormone with GHRH (GHR).

The Examiner asserts that the only difference between Bercu and the present invention is the use of the GHR analogs to release the growth hormone but that such use would have been obvious given that Gaudreau et al. and Coy et al. teach the use of GHR analogs of the present invention to release growth hormone.

Claims 1 and 16 have been rejected under 35 U.S.C. 103 as being obvious over Gaudreau et al. in view of Kann et al. Further to the teachings of Gaudreau et al., as discussed above, Kann et al. is relied on for teaching a correlation between stimulation of protein anabolism and GRF, thus making it obvious to improve protein anabolism with GRF.

Claims 1 and 15 have been rejected under 35 U.S.C. 103 as being obvious over Gaudreau et al. in view of Recker. Further to the teachings of Gaudreau et al., as discussed above, Recker is relied on for teaching a method of treating osteoporosis with GRF.

Claims 1 and 17 have been rejected under 35 U.S.C. 103 as being obvious over Gaudreau et al. in view of Clark. Further to the teachings of Gaudreau et al., as discussed above, Clark is relied on for teaching a correlation between lipolytic effect and GH. Thus, the Examiner asserts it would have been obvious to use GRF to induce GH secretion which inturn stimulates the lipolytic effect.

Applicants traverse these rejections and withdrawal thereof and reconsideration and allowance of the claims are respectfully requested.

The unobviousness of the present invention over the prior art has been discussed above with regard to Gaudreau et al. Those arguments are equally applicable herein.

As noted above, the experimental data of the declaration of Dr. Brazeau compares alkane-based compounds of Gaudreau et al. with the equivalent compound of the present invention having a double bond and further compares compounds of the prior art having either four or eight carbon main chains to a compound having six carbons.

As evidenced by Experiments 1 and 2, both the chain length and the presence of a double bond contribute to the unexpected, unobvious superior activity of the present compounds over those of the prior art.

The prior art in no way discloses or suggests fatty body-pro-GRF compounds having a double bond and a linear main chain of between 5-7 carbons. Gaudreau et al. disclose alkane based compounds of 3, 4, 6 or 8 carbons and Coy et al. only disclose acetyl based compounds. In neither Gaudreau et al. nor Coy et al. is there any suggestion of alkene based compounds having 5 to 7 carbons or of the superior activity possessed thereby.

There is additionally no suggestion of compounds of the present invention having a main chain length of 5 to 7 carbons and a double bond in the cited references of Felix et al., Bercu et

al., Kann, Recker or Clark. As such, the secondary references do not make up for the deficiencies in the teachings of Gaudreau et al. or Coy et al. to in anyway suggest the present invention.

As the present alkene fatty body pro-GRF compounds having 5 to 7 carbons in the main chain have unexpected, unobvious superior activity over the compounds of the prior art, the present invention is clearly not obvious over the prior art. Withdrawal of the rejection is thereby requested.

Double-patenting rejection

Claims 1-18 have been rejected with a provisional obviousness-type double patenting rejection over copending application serial No. 08/702,114. Applicants respectfully request that this matter be held in abeyance until such time as one application is deemed allowable at which time a terminal disclaimer will be filed as appropriate.

As the above-indicated amendments and remarks address and overcome the rejections of the Examiner, withdrawal of the rejections and allowance of the claims are respectfully requested. Should the Examiner have any questions regarding the above-indicated application he is requested to contact MaryAnne Liotta, PhD (Reg No. 40,069) in the Washington DC area at (703) 205-8000.

Serial No. 08,702,113

Please charge any fees or credit any overpayment pursuant to 37 C.F.R. 1.16 or 1.17 to Deposit Account No. 02-2448.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

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